Myocardial $^{201}$TI washout after combined dipyridamole submaximal exercise stress: Reference values from different patient groups

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Abstract. Dipyridamole stress is favorable in patients unable to exercise maximally for $^{201}$TI myocardial scintigraphy. Aside from an analysis of uptake defects, proper washout analysis can be limited by heart rate variations when isolated dipyridamole stress is used. Heart rate standardized $^{201}$TI washout kinetics after a combined dipyridamole and submaximal exercise stress protocol (CDSE), feasible in elderly patients as well as in patients with peripheral artery disease, were therefore studied to investigate the $^{201}$TI washout after CDSE in differently defined patient groups: Group I comprised 19 patients with documented heart disease and angiographically excluded coronary artery disease (CAD); group II contained 17 patients with a very low likelihood of CAD determined by both normal exercise radionuclide ventriculography and normal $^{201}$TI uptake. Group III comprised 56 patients with a 50% pretest likelihood of CAD but normal $^{201}$TI uptake. Mean washout values were nearly identical in all groups. Despite similar uptake patterns, however, washout standardized by CDSE was significantly lower than the normal washout values after maximal treadmill exercise. Thus an obviously lower $^{201}$TI washout after CDSE than after maximal treadmill exercise must be considered if washout analysis criteria after dipyridamole are applied to evaluate ischemic heart disease. Nevertheless, heart rate elevation achieved by additional submaximal exercise stress seems necessary, adequate and clinically safe for standardisation of washout analysis in dipyridamole $^{201}$TI scintigraphy.

Key words: Myocardial scintigraphy – $^{201}$TI washout – Combined stress – Dipyridamol – Submaximal exercise

Inclusion of washout analysis into quantitative analysis of $^{201}$TI myocardial scintigraphy has been proposed to improve the accuracy of sequential stress delayed TI scintigraphy in the detection of three vessel disease, and for non invasive localization of diseased vessels. This was investigated using maximal treadmill exercise prior to injection of $^{201}$TI and comparing circumferential washout profiles with lower normal limits created by TI imaging in individuals with a very low pretest likelihood of coronary artery disease (Garcia et al. 1981; Bateman et al. 1984; Kaul et al. 1986). It was demonstrated that subsequent TI washout depends on the maximum heart rate achieved during the stress test (Kaul et al. 1986), thus limiting the value of washout analysis if the achieved heart rate is not taken into account as a decisive criterion after submaximal exercise.

In patients unmotivated or unable to attain maximal exercise, vasodilation by intravenous dipyridamole was proposed as a valuable stress test to analyse only uptake defects in $^{201}$TI scintigraphy for detection of coronary risk (Boucher et al. 1985; Leppo et al. 1984). Parallel results have been reported for sensitivity and specificity in diagnosing coronary artery disease compared to maximal exercise stress (Josephson et al. 1982; Iskandrian et al. 1985). The combination of submaximal exercise and oral pharmacologic dipyridamole stress further increases sensitivity (by uptake defects) as compared to exercise stress alone (Walker et al. 1986). This, together with preliminary experience using dipyridamole alone, prompted us to conclude that pharmacologic vasodilation combined with simultaneous heart rate standardised submaximal bicycle exercise is a valuable approach for investigation of TI washout. In order to gather experience for the clinical use of refined quantitative analysis, $^{201}$TI washout patterns were studied in different patient groups, presumably not having coronary artery disease.

Methods

Patients

Three hundred and nine patients with suspected CAD consecutively underwent $^{201}$TI myocardial scintigraphy following combined dipyridamole submaximal bicycle exercise (CDSE) test for evaluation of chest pain. Of these, 92 were selected according to the following criteria: Group I comprised 19 patients with different heart diseases (cardiomyopathy, valve replacement, post myocarditis), coronary artery disease was excluded by coronary angiography within three months of the investigation. Group II consisted of 17 patients with normal initial TI uptake and normal left and right ventricular function and wall motion as assessed by exercise equilibrium radionuclide ventriculography indicating a very low likelihood of CAD (Iskandrian et al. 1986; Rozanski et al. 1985). Group III included all 56 patients with a 50% pretest likelihood according to their symptoms and risk factors, but with normal initial visual $^{201}$TI uptake that suggested an absence of coronary artery disease in the majority of these patients according to the sensitivity of the initial $^{201}$TI uptake (Josephson et al. 1982); this patient group was classified as having a low likelihood of CAD according to non invasive testing and risk analysis (Dia-
After withdrawal of beta blocking agents and coronary active drugs in the overnight fasting patient, a flexible intravenous line was installed in an antecubital vein continuously rinsed by a physiologic saline solution. When the test was started with the patient in the supine bicycle position, 0.5 mg dipyridamole/kg body weight was injected over a period of 4 min in 1 min increments. Immediately after injection of dipyridamole the patient started pedalling at a workload of 25 to 50 W. Workload was then modified to achieve a target heart rate close to 115/min (75% of the average age predicted heart rate; 200 minus age – the expected heart rate in supine position); this heart rate level was chosen arbitrarily to be easily achievable by patients that are not able to exercise well. Three min after the dipyridamole injection was terminated, but still during bicycle exercise, $^{201}$TI was injected as a bolus according to the patient's body weight (2 mCi in a 67 kg patient) and was then flushed with 20 ml saline solution. Pedalling was continued for one more min to terminate the stress test (Fig. 1). Heart rate and blood pressure were monitored during the test.

$^{201}$TI myocardial scintigraphy

**Imaging and analysis.** Myocardial scintigraphy was started 6 min after injection of $^{201}$TI (5 min after termination of exercise) in the anterior, LAO and steep LAO projection, exactly as proposed by Garcia (Garcia et al. 1981); and used in a multicenter trial (Van Train et al. 1986). A large field of view gamma camera (Siemens ZLC 370) equipped with a high resolution collimator was used for dual peak imaging. A 25% window was centered on the lower $^{201}$TI X-ray peak and another, independent, 15% window covered the 167 keV photopeak. A hardware zoom was used to acquire images in a $128 \times 128$ matrix to obtain computer images equal in size to non zoomed imaging by a standard field of view gamma camera. Acquisition time was 10 min for each view. Early (initial) and 4 h (delayed) images were acquired (Fig. 1).

**Image processing.** Besides visual assessment of initial uptake from two differently exposed X-ray charts, we performed a quantitative computerised analysis of images to create individual circumferential uptake and washout profiles with a program originally supported by the Cedars Sinai Medical Center using a MDS-A**2** Computer System. In short, after interpolative background subtraction as well as pre-processing with a 9 point weighted filter, the program generated maximum count circumferential profiles by searching along 60 radii separated by 6° intervals. Maximum count values were plotted clockwise from 0° to 360°, with the apex aligned at 90°. The program normalized the profiles to 100% for maximum counts and computed circumferential percentage washout profiles from the initial to delayed uptake profiles. Additionally, the program allows creation of pooled files of mean uptake and washout values in each view with their respective standard deviations for different patient populations. These values can be displayed graphically. By changing the number of standard deviations, the upper and lower limits of the normal range can be varied. Supported by the inventors of the program, our program version additionally comprised the fixed normal uptake and washout ranges (mean +/-2.5 standard deviations) obtained in 49 patients (personal communication by K. Van Train) with a very low likelihood of coronary artery disease (Van Train et al. 1986). These values were obtained using maximal treadmill exercise stress before myocardial scintigraphy. The mean washout values, standard deviations and numbers of patients in our three patient groups were used for inter group comparison and were compared with the values of the Los Angeles Cedars Sinai Medical Center, which evaluated a normal population with identical computer processing.

**Statistical analysis.** Statistical vectors of variables in different patient groups were used for one way analysis of variance using the Student Newman Keuls test to search for significant differences between the groups (SPSSPC + statistical software).

**Results**

The demographic data of the different patient groups under investigation (Table 1) did not reveal significant differences. Hemodynamic variables at the time of thallium injection were not significantly different between the groups (Table 2).

**$^{201}$TI washout**

The pooled circumferential uptake values with lower and upper limits derived by display of mean +/-2.5 standard deviations as well as the corresponding washout values for the investigated patient groups are shown in comparison with the circumferential profiles created by identical computer processing of the normal population after maximal treadmill exercise investigated at the Cedars Sinai Medical Center. The demographic characteristics of the patient population are summed up in Table 1.

### Table 1. Demographic characteristics of study population groups

<table>
<thead>
<tr>
<th>Group</th>
<th>$N$</th>
<th>Mean age</th>
<th>Age range</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>19</td>
<td>61</td>
<td>35–73</td>
<td>$F=7, M=12$</td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>47</td>
<td>35–63</td>
<td>$F=7, M=10$</td>
</tr>
<tr>
<td>III</td>
<td>56</td>
<td>52</td>
<td>37–67</td>
<td>$F=26, M=30$</td>
</tr>
</tbody>
</table>

* No significant differences between the groups could be established.

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**Combined dipyridamole and submaximal bicycle exercise stress protocol (CDSE)**

Myocardial scintigraphy was started 6 min after injection of $^{201}$TI (5 min after termination of exercise) in the anterior, LAO and steep LAO projection, exactly as proposed by Garcia (Garcia et al. 1981); and used in a multicenter trial (Van Train et al. 1986). A large field of view gamma camera (Siemens ZLC 370) equipped with a high resolution collimator was used for dual peak imaging. A 25% window was centered on the lower $^{201}$TI X-ray peak and another, independent, 15% window covered the 167 keV photopeak. A hardware zoom was used to acquire images in a $128 \times 128$ matrix to obtain computer images equal in size to non zoomed imaging by a standard field of view gamma camera. Acquisition time was 10 min for each view. Early (initial) and 4 h (delayed) images were acquired (Fig. 1).